REMARKS

All the claims submitted for examination in this application have been rejected and/or objected to. Applicants have amended their claims and respectfully submit that all the claims currently in this application are patentable over the objection and rejections of record.

Turning first to the sole ground of objection, Claim 22 stands objected to insofar as the term "a Na/Ca exchanger modulators" is grammatically incorrect.

Applicants have amended Claim 22 to make it clear that the term --a Na/Ca exchanger modulator-- was intended. That is, the recited cardiovascular agent is recited in the singular. Indeed, many of the recited cardiovascular agents of Claim 22 have been amended to be consistent with this model of reciting agents in the singular. It is thus emphasized that the amendment of Claim 22 is totally irrelevant to patentability and is solely intended to better linguistically express the invention of that claim.

An identical amendment has been made to Claim 19. This amendment is also totally irrelevant to patentability.

Five formal grounds of rejection have been imposed in the outstanding Official Action. The first of these directed to Claims 1 to 13. Claims 1 to 13 stand rejected, under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specific basis of this first ground of rejection is that the written description standard set forth in University of California v. Eli Lilly and Co., 119 F.2d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) has not been met. In support of this contention, the Official Action avers that the examples are limited to 3-deoxy-3-aminoribouronic acid and

amide compounds and does not describe any other 5-functionality in place of carboxyl or carboxamide or any other alternative membered ring in place of ribofuranosyl (variable X = O). Further support for this ground of rejection is provided by the alleged excessive breadth of the definitions of variables G, R^4 and "R^4 and R^5" taken together.

Applicants have considered this ground of rejection and respectfully submit that the basis for this ground of rejection is unsustainable.

A review of the portion of the University of California ruling relied upon in the outstanding rejection is directed to generic formulae in which genetic material is recited. As a general rule, however, the University of California decision holds that a generic formula is normally an adequate description of the claimed genus. This is so insofar as one skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompasses.

So it is in the present application. The generic formula, Formula I, identifies all the compounds encompassed therein. Certainly, the 36 species reduced to practice in accordance with generic Formula I sustains this position. In addition, the inclusion of methods of forming compounds within the scope of Formula I insure that those skilled in the art understand the scope of species within the contemplation of the generic formula set forth in Claim 1, from which Claims 2 to 5 and 7 to 12 ultimately depend.

The University of California case applies only to claims directed to genetic material which does not provide an adequate written description of the genus. However, the genus in the present application, Formula I, is clearly set forth in Claim 1 and those skilled in the art recognize the identity of species of this genus independent of the number of compounds reduced to practice as set forth in the specification of this application.

That the specification also provides three schemes for synthesizing compounds within the generic formula of Claim 1 establishes that the recited generic formula is more than adequate to meet the written description requirements of 35 U.S.C. §112, first paragraph.

It is noted in passing that the limitations of Claims 2 to 5 further restrict the meaning of the radicals set forth in independent Claim 1. As such, these claims are even further removed from the basis for this written description rejection imposed in the outstanding Official Action.

It goes without saying that Claim 6 is directed to a Markush group of compounds. That Claim 6 is independent and does not include a generic formula emphasizes the inappropriateness of rejection of this claim predicated upon the absence of an adequate written description.

A second formal ground of rejection is directed to Claims 1 to 13. This second ground rejects Claims 1 to 13, under 35 U.S.C. §112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The basis for this enablement type rejection is predicated upon the criteria set forth in In re Wands, 858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Suffice it to say, Wands sets forth minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate.

The first basis for this enablement rejection is that the breadth of the claims is excessive, specifically, because of the presence in Claims 1 to 6 of the wide definition of variables S, Z, R^1, B, G, R^4, R^4 and R^5 taken together and R^{B1}-R^{B5}.

To begin with, this basis for rejection does not include Claim 6 which, as stated above, is nothing more than a Markush group of specific species which does not include any variables. However, it is also emphasized that the rejection of Claims 1 to 5, which do contain the objected to radicals, are fully enabled by the specification.

The University of California decision establishes conclusively that a generic formula where the radicals are fully defined meets the description test. That it also meets the enablement test of 35 U.S.C. §112, first paragraph is established by the portion of the specification which describes processes for the manufacture of the compounds. Specifically, Pages 21 to 30 of the specification describe methods of manufacture of compounds within the scope of the generic formula of Claim 1. These methods utilize the radicals defined in Claim 1. As such, the large number of definitions of the variables does not affect the difficulty of making these compounds. That is, the specification provides an adequate disclosure such that the amount of experimentation required to generate any of the compounds within the generic formula of Claim 1 is not excessive. It is clear that the aforementioned portion of the specification permits those skilled in the art to manufacture any of the species within the contemplation of the present invention without undue experimentation.

As far as the second basis for absence of enablement is concerned, the alleged total absence of any test data in support of the method of Claims 7 to 11, it is noted that the Official Action admits that the state of the prior art with regard to methods of reducing tissue damage caused by ischemia or hypoxia is well developed. As such, the well developed nature of the state of the prior art does not necessitate amplification of the method of Claims 7 to 11.

Applicants point to subparagraph H, at pages 4 and 5 of the Detailed Action of the outstanding Official Action. Therein it is admitted that the experimentation needed to make

or use the invention based on the content of the disclosure is substantially absent in regard to the chemical synthesis of specific embodiments. What is objected to is the alleged unacceptable level of unenabled variables and/or unenabled substituents on other layers of substitution.

Applicants submit, however, that the schemes set forth at Pages 21 to 30 of the specification apply to all the meanings of the variables recited in Claim 1. Thus, the fact that there can be a multiplicity of meanings does not in any way affect the synthesis methods set forth in the specification. These methods, e.g., Schemes I, II, and III, inform those skilled in the art how to synthesize any compound, independent of the meanings of the radicals, within the meaning of Formula I.

To sum up the above remarks, the requirements set forth in Wands are met by the specification of the present application and Claims 1 to 13 are fully enabled under 35 U.S.C. §112, first paragraph.

The third formal ground of rejection is closely related to the second ground of formal rejection. The third formal ground of rejection is directed to Claims 14 to 23. Claims 14 to 23 stand rejected, under 35 U.S.C. §112, first paragraph, as containing subject matter not enabled by the specification.

Again, the criteria set forth in Wands is submitted by the Official Action to not be met by Claims 14 to 23. Although the Official Action, in making this rejection, fails to define the claims within the scope of Claims 14 to 23, it is noted that these claims are directed to pharmaceutical compositions which include a compound within the scope of Claim 1, a second compound which is a cardiovascular agent, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor or an aldose reductase inhibitor and a pharmaceutical carrier

therefor. Suffice it to say, Claims 14 to 23 are directed to a pharmaceutical composition containing the aforementioned components; a method of reducing tissue damage resulting from ischemia or hypoxia by administering this composition to a mammal, or a pharmaceutical kit which includes this composition.

The basis for the allegation that undue experimentation is required to practice the invention of these claims is predicated upon the absence of substantial prior art directed to the utilization of the second recited ingredient in the treatment of hypoxia or ischemia-induced damage in cardiac tissue.

The Official Action, by the absence of any recitation of the absence of non-utilization of compounds of the type defined in Claim 1 in the treatment of ischemia or hypoxia induced cardiac damage, argues that the use of such compounds in this utility is appreciated in the prior art. As such, working examples are not required to establish that such compounds are useful in the treatment of ischemia or hypoxia, as claimed in Claims 14 to 23.

Turning then to the Official Action argument that the use of the second component in this type of treatment is not well known, the requisite degree of knowledge is admitted to exist, as established by the disclosure of the publication brought to the attention of the PTO, the disclosure in International Application No. WO 01/23399. That disclosure provides evidence of the knowledge in the art of treating ischemia or hypoxia damage with compounds of the type recited as the second component of Claims 14 to 23.

The Official Action, in dismissing the WO 01/2399 disclosure, which is commonly assigned, attempts to bypass the clear rules of Wands by arguing that the disclosure of ischemia and hypoxia, utilizing a second compound, as set forth in subparagraph (b) of Claim 14, is derived from applicants' own work.

Applicants challenge this analysis. The work in question has been published. References available to those skilled in the art evidence knowledge in the art of the disclosure included therein. As such, treatment of hypoxia/eschemia-induced damage in cardiac tissue is known in the art and thus the requirement that there be working examples exemplifying this method of treatment is unnecessary given that the state of the art has developed to the point where those skilled in the art are aware of the claimed method.

It is noted in passing that the arguments advanced in subparagraph E, at Page 6 of the Detailed Action, wherein it is stated that the level of predictability in the art is relatively high when a single adenosine-isoteric compound is administered to treat cardiac-circulatory tissue for a variety of ailments rebuts this ground of rejection. However, the proviso made in that subparagraph, that it would not be known in a treatment utilizing a compound in accordance with subparagraph (b) of Claim 14, is rebutted by the fact that applicants' own work is representative of the prior art and establishes that it is indeed known in the art.

The final formal ground of rejection is directed to Claims 1 and 2. These claims stand rejected, under 35 U.S.C. §112, second paragraph, as being indefinite.

The first basis for this indefiniteness rejection resides in the meaning of R^1 as carbamoyl. The Official Action argues that "carbomoyl" is both incomplete and indefinite. For reasons unknown to applicants, the Official Action states that the functional group is "O-carbomoyl."

Carbomoyl is the group denoted as H^2NCO-. It is this group that is intended as a meaning of R^1 and that meaning is complete. This radical is accomodatable on the ribofuronase ring at the R^1 substituent location. It is emphasized that the observation that the

alleged defect in the recitation of carbomoyl may be rejectable under 35 U.S.C. §112, first paragraph, because of the absence of exemplification, has been addressed earlier.

The second basis for the indefiniteness rejection is that the meaning of A, $-(C_mH_{2m-2})-$, does not particularly point out what is being claimed. The Official Action states that Claim 1 should be amended to indicate that the noted meaning

Applicants respectfully decline to make this amendment to Claim 1. The test of a claim is that it be understandable to those skilled in the art. That the Official Action recognizes that the linking group A must be monounsaturated or monocyclic evidences that those skilled in the art would understand these meanings of the aforementioned term. Hence, those skilled in the art are aware of the meaning of that term and that term is thus definitive. There certainly is no need to further lengthen an already long claim with further description that those skilled in the art clearly appreciate without such language.

The objection to the term "optionally linked through (C_1-C_3) alkyl" as being unclear is respectfully traversed. That term is utilized in defining R^4. R^4 has the meaning "a partially saturated, fully saturated or fully unsaturated 5 to 8 membered ring optionally linked through C_1-C_3 alkyl where R^4 has one of the five meanings of G. In each of these meanings the radical R^4 is bonded to a nitrogen atom and R^5. That is, the ring may be bonded to nitrogen or the radical R^5 through an alkyl group containing 1 to 3 carbon atoms. As such, this meaning is clear to those skilled in the art.

The penultimate basis for indefiniteness recited in this ground of rejection is the proviso recited at lines 66 to 68 of Claim 1. The Official Action, in order to insure that a prodrug, a pharmaceutically acceptable salt, a hydrate or a solvate of the compound or the

prodrug is also within the scope of the proviso requests that the proviso be placed at the very end of Claim 1.

Although applicants do not appreciate the concern exhibited in the Official Action, they have, in a spirit of cooperation, redrafted the claims so that the proviso is recited at the end of the Claim1 and the newly added independent claims.

The final ground of indefiniteness is directed to line 5 of Claim 2. Therein the meaning of (C_1-C_6) alkylcarbomyl of R^1 is deemed indefinite for the same reason given in the rejection of Claim 1 for the inclusion of carbomoyl as one of the meanings of R^1.

Applicants adopt the remarks made earlier in defending the meaning of R^1 as carbomoyl. C_1-C_6 alkycarbomoyl is a well established radical known to those skilled in the art. Applicants furthermore emphasize that this meaning of R^1 in Claim 2 is properly dependent from the meaning mono-N-(C_1-C_4) alkylaminocarbonyl of R^1 in Claim 1.

The above remarks establish that amended Claim 1 is patentable under 35 U.S.C. §112, first and second paragraphs. Reconsideration and removal of the formal grounds of rejection is therefore deemed appropriate. Such action is respectfully urged.

The first substantive ground of rejection is directed to Claims 1 to 6. Claims 1 to 6 stand rejected, under 35 U.S.C. §102(b), as being anticipated by U.S. Patent 2,852,502 to Baker et al.

The basis for this ground of rejection is that compounds within the scope of Baker et al. include Example 40, 6-benzylamino-9-(3-amino-3-deoxy-ß-D-ribofuranoxy) purine, which anticipates Claims 1 to 6.

Applicants have amended their claims to exclude the meaning where the aryl group bonded to an alkylene group is unsubstituted. This has been accomplished by removing

unsubstituted aryl from the meanings of B. In addition, the meanings of R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} are recited separately by adding new Claims 24 to 29. In none of these claims is there a meaning where all of R^{B1} to R^{B5} are hydrogen. As such, there is no meanings of the claimed compound having the formula I where unsubstituted benzyl is present.

In view of this amendment it is apparent that Claims 1 to 5 of the present application, directed to the compound having formula I, are novel over Baker et al.

It is emphasized that independent Claim 6 recites a list of specific compounds. None of these compounds include an unsubstituted benzyl group. As such, all the species within the contemplation of Claim 6 are novel.

The second substantive ground of rejection also concerns Claims 1 to 6. This ground of rejection is predicated upon the disclosure of the same compound as Example 40 in Baker et al. by any one of U.S. Patent 2,852,506 to Goldman et al.; Goldman et al., J. Med. Chem., 6 (4), 413-423 (July, 1963); or Goldman et al., J. Amer. Chem. Soc., 78 (8), 4173-4175 (Aug 20, 1956).

Applicants submit that the above remarks, directed to the response to the rejection predicated upon the Baker et al. patent, apply to the second substantive ground of rejection.

The third substantive ground of rejection is directed to Claims 1 to 6, 12 and 13. These claims stand rejected, under 35 U.S.C. §102(b), as being anticipated by Goldman et al., J. Am. Chem. Soc., 78 (8), 4173-4175 (August 20, 1956).

The Official Action states that the Goldman et al., in the paragraph bridging Pages 4174 and 4175, discloses a N^6-benzylamino compound which anticipates Claims 1 to 6, 12 and 13.

Again, the amendment to Claims 1, 2 and 5, wherein the scope of the present application excludes unsubstituted benzyl, excludes the compound of Goldman et al. from the scope of all the claims currently in this application.

The fourth substantive ground of rejection is directed to Claims 1 to 13. Claims 1 to 13 stand rejected, under 35 U.S.C. §102(b), as being anticipated by U.S. Patent 5,688,774 to Jacobson et al.

This ground of rejection is predicated upon the disclosure in Jacobson et al. at Claim 1 wherein certain of the species of the compound of that claim are within the scope of the generic compound of the Claim 1 to 13 of the present application.

Applicants respectfully submit that the amendment to Claim 1, by excluding unsubstituted aryl, and more specifically phenyl, distinguishes Claims 1 to 13 from the compound of Claim 1 of Jacobson et al.

The final substantive ground of rejection is directed to Claims 1 to 13. Claims 1 to 13 stand rejected, under 35 USC§103(a), as being made obvious by Jacobson et al.

The amendment to the claims mentioned above, wherein the radical B is excludes unsubstituted aryl, and specifically unsubstituted phenyl, not only is outside the scope of any specific compounds taught by Jacobson et al. but, in addition, is unobvious over that reference.

This is so insofar as the amended claims require substituents on the claimed phenyl ring, bonded through an alkylene group to nitrogen, and these substituents are far removed from the substituents disclosed in the corresponding generic compound disclosed by Jacobson et al. The only exception to this complete structural unobviousness is halo substituents. However, there is no disclosure or suggestion of any specific claimed compounds in the

present application which include halogen substituents taught by the Jacobson et al. compound. Indeed, all specific examples employing halogen substituents in Jacobson et al. are limited to 3-iodobenzyl. Not only are there no specific compounds disclosed in the present application where R^{B3} is iodo but, indeed, there are no compounds where all but one of R^{B1} to R^{B5} are hydrogen and the remaining substituent is halogen, let alone iodo. Indeed, this fact, is addition to the absence of any criticality to the 3-position substituted with halogen, evidences the non-obviousness of the Jacobson et al. disclosure.

The above remarks establish the patentability of the amended claims of the present application over the substantive grounds of rejection. Reconsideration and removal of these grounds of rejection is therefore respectfully solicited.

The amendment required to remove all compounds of the prior art from the scope of the claims of the present application has necessitated the introduction of nine new claims 24 to 32, in addition to the amendment of Claims 1, 2 and 5, wherein R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} are separately defined.

This amendment has, in turn, necessitated the amendment of Claims 7, 12 and 13 so that these claims contain the same scope as original Claims 1, 12 and 13.

It is emphasized that these new claims add no new matter to the application. Support for this amendment is provided by the statement that R^{B1}, R^{B2}, R^{B3}, R^{B4} and R^{B5} independently have the meanings recited therein. The present amendment merely sets forth the independent meanings of these radicals.

It is noted that the Official Action indicates that Claims 14 to 23 would be allowable if rewritten in independent form. Applicants have amended Claims 14, 19 and 23 to effectuate this result.

The above amendment and remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims, Claims 1-32, is therefore respectfully solicited.

Respectfully submitted,

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